PCT/EP2004/011960
1.10.04


INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

# PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

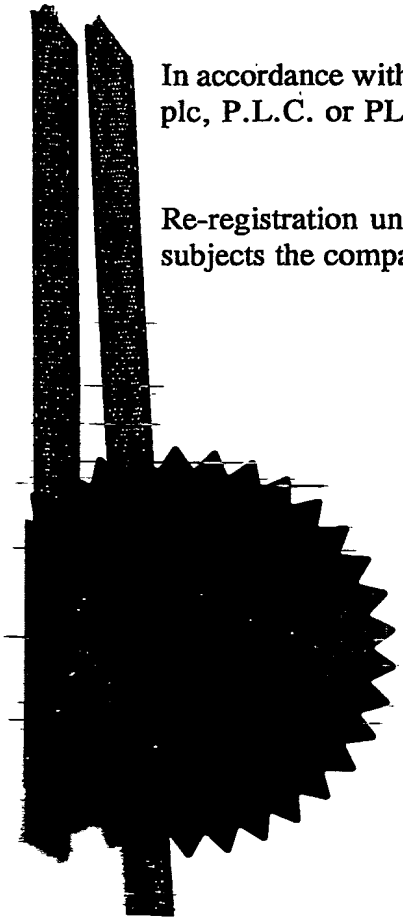


I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

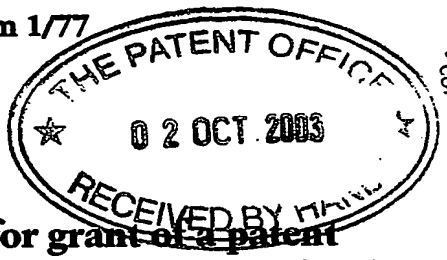


Signed Julian Morell

Dated 13 September 2004

**Patents Form 1/77**

Patents Act 1977
(Rule 16)







# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

**The Patent Office**

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference **PPD 70252/GB**

2. Patent application number *(The Patent Office will fill in this part)* 02 OCT 2003 **0323090.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   SYNGENTA PARTICIPATIONS AG
   Intellectual Property Department
   Schwarzwaldallee 215
   4058 Basel
   SWITZERLAND

   08029555001

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention **NOVEL PROCESS**

5. Name of your agent *(if you have one)*

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   **Jane Elizabeth SWIFT**
   Intellectual Property Department
   Syngenta Limited
   Jealott's Hill International Research Centre
   PO Box 3538
   Bracknell, Berkshire, RG42 6YA
   UNITED KINGDOM

   Patents ADP number *(if you know it)* 08148298002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|
| | | |

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|
| | |

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

   *a) any applicant named in part 3 is not an inventor, or*
   *b) there is an inventor who is not named as an applicant, or*
   *c) any named applicant is a corporate body.*
   *See note (d))*

   YES (b)

**Patents Form 1/77**

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

| | |
|---|---|
| Continuation sheets of this form | 03 |
| Description | 01 |
| Claim(s) | |
| Abstract | 00 |
| Drawing(s) | 00 |

CF

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application.

SYNGENTA PARTICIPATIONS AG

Signature MA Rudd Date 02/10/03

Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

Margaret Ann RUDD

**Warning**

*After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.*

**Notes**

*a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

*b) Write your answers in capital letters using black ink or you may type them.*

*c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

*d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

*e) Once you have filled in the form you must remember to sign and date it.*

*f) For details of the fee and ways to pay please contact the Patent Office.*

# NOVEL PROCESS

The present invention relates to a novel process for the preparation of 2-(2'-nitro-4'-methylsulphonylbenzoyl)-1,3-cyclohexanedione (mesotrione).

The current process for preparing mesotrione requires the reaction of cyclohexanedione with 2-nitro-4-methylsulphonylbenzoylchloride to give the enol ester, followed by a rearrangement process resulting in mesotrione. The reaction is carried out in a suitable solvent in the presence of an organic base and an appropriate catalyst. After formation of the product, the solvents are removed and the pH of the solution increased to approximately 11-12.5 by the addition of sodium hydroxide to give a suspension of the insoluble sodium enolate salt in a mixture of water and organic base. Crystallisation of the mesotrione product is effected by the controlled addition of 10% HCl down to a pH of approximately 2.8. The resulting product is then collected by appropriate means, for example using a centrifuge.

However, we have now found that following this process occasionally results in undesirable impurities being present in the final mesotrione product. A further problem with this process is that at a pH of 11-12.5, the organic base is present as the free base and is partially immiscible with the aqueous components of the mixture. It is not possible to separate the organic base from the mixture due to the presence of the solid sodium enolate of mesotrione. Similarly, it is not possible to separate any other organic immiscible solvents from this mixture or to carry out a purification process with solid phase absorbents due to the presence of solids.

Accordingly, one object of the present invention is to provide an improved process for the preparation of mesotrione that results in a purer final product.

A second object of the invention is to provide a method of purifying mesotrione (prepared by any method) to result in a purer final product.

Accordingly, the present invention provides a process for the preparation of mesotrione, said process comprising the steps of:

(i) reaction of cyclohexanedione with 2-nitro-4-methylsulphonylbenzoylchloride in an appropriate solvent and in the presence of an organic base to give the enol ester,

(ii) rearrangement of the enol ester to give mesotrione,

(iii) removal of the solvent, and thereafter

(iv) formation of a soluble enolate salt of mesotrione,

(v) one or more purification steps, and

(vi) crystallisation of mesotrione.

In another aspect of the invention, there is provided a process for the purification of mesotrione, said process comprising the steps of:

(i) formation of a soluble enolate salt of mesotrione,

(ii) one or more purification steps, and

(iii) crystallisation of mesotrione.

The process for the reaction of cyclohexanedione and 2-nitro-4-methylsulphonylbenzoylchloride and the rearrangement reaction may be carried out as described in EP0186117, and which is incorporated herein by reference.

The formation of a soluble enolate salt of mesotrione may be carried out by the addition of a suitable second base to the mesotrione-containing solution. Examples of suitable bases include, but are not limited to, potassium hydroxide, ammonium hydroxide, pyridine and triethylamine. Most preferred is potassium hydroxide.

The purification process may include one or more purification steps, carried out in any order. Examples of suitable purification steps include, but are not limited to the following:

1) removal of the organic base (either by a batch or a continuous method) prior to the crystallisation step. This results in improved purification, since any impurities which are soluble in the organic base, but insoluble in the aqueous phase are removed. It is also possible to add additional quantities of the organic base and perform multiple extractions to further improve the purification. Since the organic base can be removed prior to crystallisation, this also minimises the organic load of the mesotrione solution in the next process steps

2) the addition of an immiscible solvent to the enolate solution. Any impurities soluble in this solvent will then be removed with the removal of the solvent prior to crystallisation. Examples of suitable solvents include, but are not limited to, chlorobenzene, toluene, anisole, 1,2-dichloroethane, n-butyronitrile, iso-butyronitrile, benzonitrile, tetrahydrofuran, o-xylene, mixed xylenes,

3) treatment of the mesotrione enolate solution with a solid absorbent, for example activated charcoal, silica, alumina, zeolites, etc.

Crystallisation may be carried out by any method known in the art, for example by reducing the pH of the solution by the controlled addition of HCl.

The process of the invention results in a cleaner mesotrione product with less undesirable impurities.

A further advantage of the process of the present invention is that the crystallisation process is from a homogenous mixture, which will result in a more robust crystallisation process and improved operability (e.g. better pH control).

Claims

1. A process for the preparation of mesotrione, said process comprising the steps of:
   (i) reaction of cyclohexanedione with 2-nitro-4-methylsulphonyl benzoylchloride in an appropriate solvent and in the presence of an organic base to give an enol ester,
   (ii) rearrangement of the enol ester to give mesotrione,
   (iii) removal of the solvent, and thereafter
   (iv) formation of a soluble enolate salt of mesotrione,
   (v) one or more purification steps, and
   (vi) crystallisation of mesotrione.

2. A process for the purification of mesotrione, said process comprising the steps of:
   (i) formation of a soluble enolate salt of mesotrione,
   (ii) one or more purification steps, and
   (iii) crystallisation of mesotrione.

3. A process according to any one of claims 1 or 2, wherein the formation of the soluble enolate salt is carried out by addition of a second base to the mesotrione-containing solution.

4. A process according to claim 3, wherein the second base is selected from the group consisting of potassium hydroxide, ammonium hydroxide, pyridine and triethylamine.

5. A process according to claim 4, wherein the second base is potassium hydroxide.

6. A process according to any one of claims 1 or 2, wherein the purification step includes one or more of the following: removal of the organic base; addition of an immiscible solvent to the enolate solution; treatment of the enolate solution with a solid absorbent.